

CARDIOVASCULAR MEDICINE

Amino-terminal propeptide of type III procollagen is associated with restrictive mitral filling pattern in patients with dilated cardiomyopathy: a possible link between diastolic dysfunction and prognosis

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Objective: To analyse the relation between restrictive mitral pattern, amino-terminal propeptide of type III procollagen (PIIINP), and prognosis in patients with dilated cardiomyopathy.

Design: Prospective cohort study of 106 patients with dilated cardiomyopathy.

Setting: Tertiary care centre.

Main outcome measures: PIIINP concentration, echocardiographic variables, oxygen consumption, hospitalisation for heart failure, and cardiac mortality were evaluated in patients grouped by the presence of non-restrictive (group 1), reversible (group 2), and irreversible restrictive mitral pattern (group 3).

Results: Groups differed regarding left ventricular ejection fraction (group 1, mean (SD) 36 (6)%, group 2, 29 (8)%, group 3, 25 (6)%; $p = 0.0001$), left atrial ejection fraction (group 1, 0.47 (0.1)%, group 2, 0.43 (0.2)%, group 3, 0.26 (0.1)%; $p < 0.0001$), and PIIINP ($p = 0.001$). Multivariate analysis showed that PIIINP was related to mitral pattern (odds ratio 0.8, 95% confidence interval 0.23 to 1.4, $p = 0.006$) independently of left atrial and ventricular ejection fractions. After 21 months, survival was 88% and 34% ($p = 0.0001$) in patients with non-restrictive and irreversible restrictive mitral patterns, respectively.

Conclusion: In patients with dilated cardiomyopathy, restrictive mitral pattern is associated with higher PIIINP and worse prognosis.

In patients with chronic heart failure caused by dilated cardiomyopathy (DCM), restrictive ventricular filling (RF) is an important hallmark of the severity of the disease.¹ An RF pattern reflects increased left ventricular stiffness² and filling pressure³ and is a powerful marker of poor prognosis independently of ejection fraction and heart failure symptoms.^{1,4} RF is strongly load dependent but its reversibility with unloading is unpredictable and this accounts for different outcomes.⁵ The determinants of the different responses to unloading are unknown. Mitral Doppler parameters have frequently been studied in relation to symptoms or to cardiac haemodynamic factors, but rarely to the qualitative changes of myocardial tissue. However, myocardial histological changes, including extracellular collagen deposition, strongly affect left ventricular diastolic properties. In patients with heart failure, this is a consequence of the hormonal and immune activation, particularly of angiotensin II, aldosterone, and cytokines,^{6,7} which are considered to be the key factors in the progression of left ventricular dysfunction and heart failure.

The amino-terminal propeptide of type III procollagen (PIIINP) is an extension peptide of procollagen type III, which is cleaved off during conversion from type III procollagen to type III collagen. PIIINP reflects myocardial fibrosis, which is higher in the tissue of dilated and dysfunctional left ventricles.^{8,9} Importantly, increased PIIINP concentrations account for decreased survival in patients with DCM.⁸ However, no previous studies have analysed the relation between increased collagen turnover and diastolic function, as assessed by Doppler echocardiography, in patients with DCM.

The present study was planned to analyse whether PIIINP concentration may be associated with the degree of ventricular diastolic dysfunction. We hypothesised that patients

with irreversible RF with unloading are characterised by increased PIIINP concentration and worse prognosis.

METHODS

Study population

We studied 106 consecutive patients in a stable clinical status who were followed up at our outpatient heart failure clinic. All patients had a left ventricular ejection fraction $< 45\%$ and heart failure for at least six months. Exclusion criteria were an acute coronary event within the previous six months; organic mitral disease; aortic valve disease with more than mild aortic regurgitation as assessed by colour Doppler echocardiography; and presence of chronic atrial fibrillation or cardiac rhythm induced by a permanent pacemaker. Patients with chronic liver disease, pulmonary fibrosis, or rheumatoid arthritis were also excluded, since these conditions are known to be associated with increased serum concentration of PIIINP. The protocol was approved by the local ethics committee and each patient provided written informed consent.

Follow up information was obtained from clinical records, death certificates, and correspondence until 15 June 2001. The clinical end points of follow up were death and hospitalisation for heart failure.

Blood sampling

Venous blood samples were drawn on the day of the study after a 30 minute supine rest in a fasting state between 8 and

Abbreviations: CI, confidence interval; DCM, dilated cardiomyopathy; PIIINP, amino-terminal propeptide of type III procollagen; RF, restrictive ventricular filling; $\dot{V}O_2$, oxygen uptake

9 am. The concentrations of aldosterone and renin were measured by a sandwich radioimmunoassay (Biochem ImmunoSystem, Bologna, Italy). Plasma noradrenaline (nor-epinephrine) and adrenaline (epinephrine) concentrations were measured by high performance liquid chromatography with electrochemical detection. Concentrations of PIIINP in plasma were determined by radioimmunoassay with commercially available kits (Orion Diagnostica, Espoo, Finland).

Echocardiography

A complete Doppler echocardiographic examination was performed within one hour of blood sampling. Left ventricular end diastolic and end systolic volumes (monoplane four chamber apical view, area-length method) and ejection fraction were measured. Left ventricular mass was measured by M mode echocardiography as previously described.¹⁰ The mitral inflow recording was obtained by placing the pulsed Doppler sampling volume at the tip of the mitral valve during diastole. Mitral inflow early diastolic (E) and late diastolic (A) wave velocities, their ratio (E:A), and E wave deceleration time were measured. Mitral filling was considered non-restrictive (non-RF) when E:A was < 1 or when E:A was between 1 and 2 and E deceleration time was ≥ 140 . RF was considered when the E:A ratio was > 2 or when E:A was between 1 and 2 and E deceleration time was < 140. Cardiac stroke volume was measured as the product of the left ventricular outflow tract annulus area and time velocity integral measured at the same level by pulsed wave Doppler. The regurgitant volume across the mitral valve was calculated as the difference between the left ventricular stroke volume and left ventricular outflow tract stroke volume. All measurements were calculated as the average of three consecutive beats. Left atrial volume was measured at ventricular end systole and at the end of atrial contraction (area-length method from the apical four chamber view). Left atrial ejection fraction was measured as the difference between the maximum and minimum volume divided by the maximum volume.

After completion of baseline measurements, patients with RF were instructed in the performance of the Valsalva manoeuvre. The strain phase of the manoeuvre was held for 10 seconds. Close to the end of the strain phase mitral inflow velocities were recorded. RF after unloading was defined according to the same criteria as at baseline. Patients with RF who maintained RF during unloading were accordingly considered to have irreversible RF. Those who did not match the RF definition during unloading were considered to have reversible RF. Patients were subsequently divided into three groups: group 1, non-RF; group 2, reversible RF; and group 3, irreversible RF.

Exercise testing

All patients underwent a symptom limited bicycle ergometer exercise test at a constant cadence of 60 rpm. A continuous ramp protocol was used in which work rate was increased by 10 W/min. Gas exchange was monitored during the exercise test with a computerised metabolic cart (Vmax 229, SensorMedics, Yorba Linda, USA). Oxygen uptake ($\dot{V}O_2$), was measured online every 10 seconds by a standard inert gas dilution technique. Peak $\dot{V}O_2$ was defined as the highest $\dot{V}O_2$ achieved during exercise.

Statistical analysis

Continuous variables are given as mean (SD). Discrete variables are reported as the number or percentage of the total. The average values of continuous variables in the three groups, defined on the basis of mitral inflow patterns, were compared by using one way analysis of variance or analysis of covariance. Post hoc comparisons were made by using

Fisher's ISD test. Frequencies were compared by using the χ^2 test. Maximum likelihood ordered logit estimation was performed to assess the determinants of mitral inflow patterns as defined by the three patient groups. Haemodynamic variables with the strongest statistical ($p < 0.005$) association with mitral inflow patterns were used in a multivariate model to assess their independent relation to the dependent variable. The relation of specific variables to mortality was investigated univariately and multivariately by using the Cox proportional hazards model. Survival rate free from hospitalisation for heart failure was estimated by the product limit Kaplan-Meier method. Groups were compared by the log rank test. A probability value of $p < 0.05$ was considered significant. A commercially available statistical software package was used (Statview 4.5, Abacus Concepts, Inc, Berkeley, California, USA).

RESULTS

Table 1 shows the clinical, echocardiographic, and hormonal characteristics of the three groups of patients. Eighty eight patients had non-RF (group 1) and 18 patients had a restrictive mitral pattern and accordingly underwent the Valsalva manoeuvre. Nine patients had reversible RF (group 2) and nine patients had irreversible RF (group 3). Group 1 patients were slightly younger and less symptomatic than those in groups 2 and 3, although the difference was not significant. However, group 1 patients had a significantly better exercise tolerance in terms of exercise duration, peak $\dot{V}O_2$, and ventilatory response to exercise. Group 2 and 3 patients had similar degrees of both clinical and haemodynamic impairment. The only haemodynamic variables significantly different between patients with irreversible and those with reversible RF were left atrial ejection fraction and stroke volume, although a large overlap was observed between the two groups. Mitral inflow Doppler parameters at baseline did not discriminate significantly between group 2 and 3 patients.

As fig 1 shows, PIIINP concentration differed significantly between the groups. Particularly, group 3 patients had a higher concentration of PIIINP (5.94 (2.2) $\mu\text{g/l}$) than both group 2 (4.98 (0.8) $\mu\text{g/l}$) and group 1 (4.5 (1.0) $\mu\text{g/l}$), whereas group 1 and 2 patients had similar concentrations. The difference in PIIINP concentration between groups 2 and 3 remained even after adjustment for ejection fraction ($p = 0.0004$).

Table 2 shows the haemodynamic and hormonal determinants of mitral inflow Doppler echocardiography (non-restrictive, reversible restrictive, and irreversible restrictive). As expected, progressively impaired diastolic function was associated with larger left ventricular volumes, more severe mitral regurgitation, and reduced left ventricular mass to volume ratio, left ventricular ejection fraction, and cardiac forward stroke volume. PIIINP concentrations were also significantly associated with the mitral inflow pattern. Higher PIIINP concentrations were more likely to be associated with the irreversible restrictive mitral pattern. Haemodynamic variables that were associated with mitral inflow pattern with $p < 0.005$ were introduced into a multivariate model. Stroke volume was not used so as to avoid multicollinearity, due to a close relation with left ventricular ejection fraction ($r = 0.35$, $p = 0.0005$). Multivariate analysis showed that PIIINP concentrations predicted mitral inflow patterns independently of the haemodynamic variables (table 3).

The multivariate analysis was run for the subgroup of patients with ischaemic cardiomyopathy (62 patients, mean (SD) age 62 (9) years, 11% women). PIIINP concentrations were strongly associated with mitral inflow pattern (odds ratio (OR) 1.2, 95% confidence interval (CI) 0.43 to 2.00,

Table 1 Clinical, haemodynamic and hormonal characteristics of the three group patients

	Group 1 (n = 88)	Group 2 (n = 9)	Group 3 (n = 9)	p Value
Age (years)	61 (9)	65 (4)	66 (6)	NS
NYHA III-IV	32%	66%	44%	NS
Noradrenaline (pg/ml)	392 (263)	534 (402)	510 (258)	NS
Adrenaline (pg/ml)	53 (36)	50 (28)	44 (18)	NS
Aldosterone (nmol/l)	0.25 (0.1)	0.29 (0.1)	0.24 (0.1)	NS
K (mmol/l)	4.3 (0.4)	4.2 (0.3)	4.4 (0.3)	NS
Na (mmol/l)	139 (3)	138 (2)	138 (3)	NS
Creatinine (μ mol/l)	101 (27)	86 (35)	99 (15)	NS
Peak $\dot{V}O_2$ (ml/kg/min)	18 (5)	13 (5)	14 (3)	0.01
$\dot{V}E-\dot{V}CO_2$ slope	36 (6)	43 (7)	45 (11)	0.0002
Duration of exercise (min)	10 (2.0)	8.3 (2.5)	8.5 (2.2)	0.02
Respiratory exchange ratio	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	NS
LV mass (g)	224 (49)	253 (16)	212 (63)	NS
Mass to volume ratio	0.94 (0.3)	0.84 (0.1)	0.68 (0.2)	0.01
Stroke volume (ml)	82 (17)	67 (17)	58 (14)*	0.02
LV end diastolic volume (ml)	253 (59)	329 (93)	325 (112)	0.01
LV end systolic volume (ml)	163 (53)	239 (91)	247 (98)	0.002
LV ejection fraction (%)	36 (6)	29 (8)	25 (6)**	0.0001
Mitral regurgitant volume (ml)	12 (15)	23 (17)	19 (19)	NS
Left atrial maximum volume (ml)	101 (39)	117 (47)	123 (25)	NS
Left atrial minimum volume (ml)	53 (25)	77 (38)	94 (26)	0.0006
Left atrial ejection fraction (%)	0.47 (0.1)	0.43 (0.2)	0.26 (0.1)*	<0.0001
E (m/s)	0.6 (0.1)	0.8 (0.1)	0.9 (0.1)	0.0007
E:A	0.9 (0.3)	1.6 (0.6)	2.2 (0.9)*	<0.0001
E wave deceleration time (ms)	233 (73)	136 (19)	119 (5)	0.0001

Data are mean (SD).

* $p < 0.05$, ** $p = 0.09$ group 3 versus group 2 by analysis of variance.A, late diastolic wave velocity; E, early diastolic wave velocity; LV, left ventricular; NS, not significant; NYHA, New York Heart Association functional class; $\dot{V}E-\dot{V}CO_2$, minute ventilation-carbon dioxide production; $\dot{V}O_2$, oxygen uptake.

$p = 0.002$) independently of left ventricular ejection fraction (OR -0.17 , 95% CI -0.28 to -0.06 , $p = 0.003$) and left atrial ejection fraction (OR -0.04 , 95% CI -0.1 to 0.02 , $p = 0.2$).

Survival analysis

The overall population was followed up for 524 (138) days. Seventeen patients reached the end points: seven patients died and 10 were hospitalised for worsening heart failure. Kaplan-Meier analysis showed a different outcome for patients according to mitral inflow pattern (fig 2). Particularly, group 1 patients had a 90% survival rate as against 38% in group 3 after 600 days of follow up, with intermediate results for group 2 patients. The Cox multivariate proportional hazard model showed an independent

predictive value of mitral inflow pattern (hazard ratio 2.5, 95% CI 1.46 to 4.3; $p = 0.001$) and PIIINP concentrations (divided according to the median value; hazard ratio 3.0, 95% CI 1.06 to 8.74; $p = 0.04$).

DISCUSSION

The present study showed that in patients with DCM, the degree of diastolic dysfunction is associated with PIIINP concentrations independently of left ventricular volume and ejection fraction. Patients with the extreme diastolic dysfunction characterised by irreversible RF with unloading had the highest PIIINP concentrations and the worst prognosis.

The pathophysiology underlying RF is strictly linked to left ventricular stiffness,^{2,11} which is greatly increased in the last stages of experimentally induced DCM,¹² besides prolonged relaxation. The non-linear shape of the pressure-volume curve implies increased diastolic pressure when left ventricular remodelling takes place. Nevertheless, the position and the slope of that curve are strongly influenced by the histological characteristics of the myocardium.¹³

There is increasing evidence that circulating concentrations of procollagen peptide fragments and of metalloproteinases can be used as markers for myocardial collagen turnover.¹⁴⁻¹⁶ PIIINP is the most frequently studied marker. A significant correlation between PIIINP concentration and tissue collagen has been found in patients with DCM.¹⁷ Interestingly, in this population high PIIINP concentrations were associated with a poor outcome.⁸ The relation between PIIINP and diastolic function evaluated by Doppler echocardiography has not been studied in patients with DCM, to the best of our knowledge. There have been only a few investigations of the relation between mitral filling pattern and myocardial tissue properties in patients with DCM. Pinamonti and colleagues¹ found a higher, although not significant, degree of fibrosis in patients with the RF pattern. Nevertheless, semiquantitative analysis of myocardial fibrosis may mask the association with mitral inflow pattern. Furthermore, the patient population of

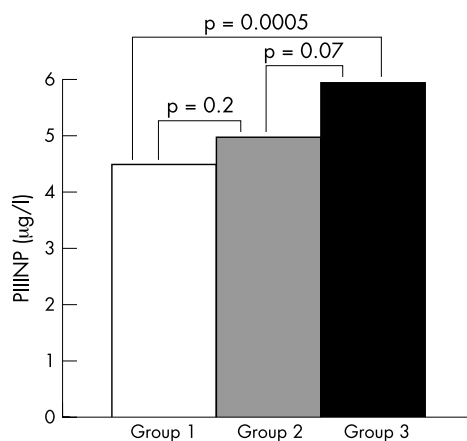


Figure 1 Concentrations (μ g/l) of amino terminal propeptide of type III procollagen (PIIINP) in the three groups of patients with dilated cardiomyopathy. Group 1, non-restrictive ventricular filling (RF); group 2, reversible RF; group 3, irreversible RF.

Table 2 Haemodynamic hormonal and structural determinants of mitral inflow patterns in the univariate analysis

	Coefficient (95% CI)	p Value
Age	0.08 (0.05 to 0.15)	0.04
Noradrenaline	0.001 (−0.0002 to 0.003)	NS
Adrenaline	−0.007 (−0.02 to 0.01)	NS
Left ventricular mass (g)	−0.002 (−0.01 to 0.0068)	NS
Stroke volume (ml)	−0.06 (−0.09 to −0.02)	0.003
LV end diastolic volume (ml)	0.005 (0.0001 to 0.01)	0.04
LV end systolic volume (ml)	0.007 (0.001 to 0.01)	0.02
LV ejection fraction (%)	−0.14 (−0.22 to −0.068)	<0.0001
Mitral regurgitant volume (ml)	0.04 (0.0055 to 0.07)	0.02
LV mass/volume	−4.4 (−7.7 to −1.2)	0.007
Left atrial ejection fraction (%)	−0.92 (−1.4 to −0.04)	<0.0001
PIIINP (μg/l)	0.68 (0.2 to 1.14)	0.003

CI, confidence interval.

Table 3 Multivariate regression analysis showing that PIIINP is related to mitral inflow pattern independently of ventricular and atrial haemodynamic variables

	p Value	Coefficient	95% CI
PIIINP (μg/l)	0.006	0.8	0.23 to 1.4
LV ejection fraction (%)	0.001	−0.15	−0.24 to −0.06
Left atrial ejection fraction (%)	0.03	−0.06	−0.12 to −0.005

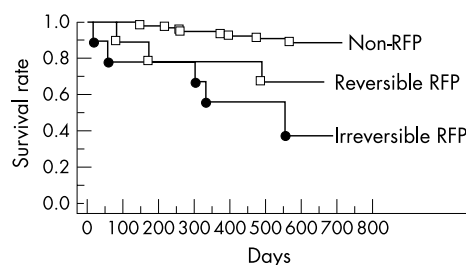
the cited study were relatively young (mean (SD) 39 (15) years). This casts doubt on the accuracy of mitral parameters in describing restrictive physiology because of the strong age dependence of the mitral pattern.

RF is a dynamic phenomenon that may change rapidly within the same patient after blood volume depletion. It has been shown that loading manipulation may induce substantial variations in mitral inflow velocities.¹⁸ However, the response may vary greatly between patients and this accounts for different outcomes.⁹ Pozzoli and colleagues⁹ showed that baseline haemodynamic variables could not predict the reversibility of RF with unloading and they hypothesised that patients with irreversible RF may have intrinsic myocardial diastolic abnormalities. Similarly, in our study there were only minor differences between irreversible and reversible RF patients at baseline haemodynamic conditions. The higher PIIINP concentration in RF than in non-RF patients was seen mainly in patients with irreversible RF. Therefore, it is likely that in patients with reversible RF, diastolic dysfunction is linked more with ventricular load than structural changes in the myocardial tissue. This may explain the relatively better outcome that was observed in this group of patients and the efficacy of drugs that have been shown to modify the myocardium at the histological level,

counteracting the renin–angiotensin–aldosterone and adrenergic systems.

An important limitation of the present study is the lack of an invasive determination of left ventricular diastolic function. Nevertheless, measurement of left ventricular stiffness includes pressure and volume determination and load manipulation during cardiac catheterisation. Such invasive testing may be unsuitable in a large cohort of patients with DCM and possibly also unethical, since the relation between RF and diastolic function is extremely well documented. There are several studies showing the strong predictive value of RF, which implies that evaluation of the determinants of RF detected by Doppler echocardiography may be clinically relevant.

It may be claimed that a non-significant difference between groups in terms of heart failure symptoms is unexpected, since most studies show that patients with RF are more symptomatic. However, our population comprised patients with stable heart failure followed up in our outpatient clinic. The percentage of patients with severe symptoms was low and the mean $\dot{V}O_2$ of the overall population was quite high (17 ml/kg/min), although the physical impairment of patients with a restrictive mitral filling pattern is best quantified by a significantly different $\dot{V}O_2$ in comparison with non-RF patients. For the same reason, the percentage of RF patients in our population is lower than in other studies where patients were sent to the heart failure unit to be selected for heart transplantation.

**Figure 2** Kaplan-Meier survival curves of patients with dilated cardiomyopathy divided into three groups according to the degree of diastolic dysfunction.

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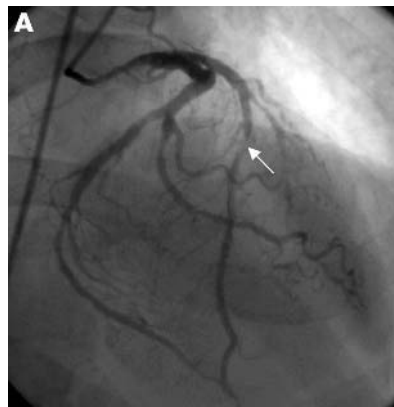
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IMAGES IN CARDIOLOGY

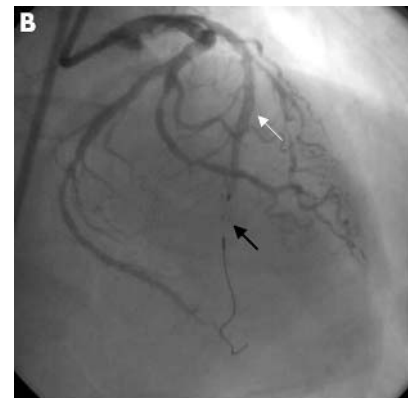
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No reflow was caught red handed in a patient with acute anterior myocardial infarction undergoing rescue angioplasty

A 58 year old male smoker who has hypertension and diabetes mellitus presented with acute anterior ST segment elevation myocardial infarction (MI). He was initially treated with thrombolytic therapy—30 mg of intravenous bolus dose of TNK-TPA (Tenecteplase, Metalyse) and heparin. A 90 minute angiogram showed a mid left anterior descending (LAD) 80% ulcerative hazy critical lesion with TIMI grade 2 flow down LAD territory (panel A). In view of ongoing chest pain, incomplete ST segment resolution, and the angiographic findings seen in this patient, rescue angioplasty (PTCA) was performed. The LAD was wired directly with a 4.0 Angioguard filter (Cordis, Johnson & Johnson Interventional Systems, New Jersey, USA) and secured in the mid to distal LAD segment. The flow down LAD territory remained the same, with TIMI 2 flow, after deployment of the filter. The mid LAD lesion was then stented directly with a 3.0 mm × 13 mm Hepacoat stent (Cordis, Johnson & Johnson Interventional Systems). The stent was further post-dilated with a 3.5 mm × 9 mm Q monorail balloon (Boston Scientific Corporation, Massachusetts, USA). This resulted in TIMI 1 flow down the LAD territory with contrast staying at the level of the opened filter (panel B), most likely due to collection of thrombotic debris embolised distally from the lesion and trapped by the filter



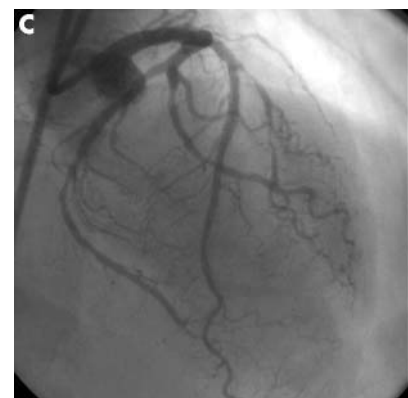
Mid LAD critical ulcerative hazy lesion (arrow) with TIMI 2 flow down LAD territory in the right anterior oblique deep cranial projection.



Post high-pressure dilatation of LAD stent (white arrow) showing TIMI 1 flow down LAD territory and stasis of contrast at the level of the opened Angioguard filter (black arrow) in the same projection.

wire. At the same time, the patient experienced more chest pain. Once the Angioguard filter was closed and retrieved, TIMI 3 flow down the LAD was restored and the patient's chest pain resolved (panel C). This case demonstrated the use of a distal protection device to prevent potentially disastrous complications in acute MI PTCA. Further clinical trials will be required to study the routine application of these types of devices in angioplasty for acute MI.

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Patent LAD stent with restoration of TIMI 3 flow down LAD territory in the same projection.